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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,507	AMARA ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *4-8,13-23,31-38 and 43-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-12,24-30 and 39-42* is/are rejected.

7)☒ Claim(s) *1,24 and 39-42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the response filed September 15, 2004, Applicant's election with traverse of Group I, HIV, is acknowledged. Applicant's arguments have been carefully considered. Applicant argues that the restriction requirement improperly limits the scope of the claims by requiring restriction between Groups I-IV. For example, Group I is drawn to a method of preventing or treating a mammal with a DC-SIGN modulator that is a derivative of an effector molecule. However, claim 1 of Group I is drawn to a method that uses a generic DC-SIGN modulator, whereas claim 3 recites that the modulator is a derivative of an effector molecule. Therefore, the Office has improperly limited the claims to certain embodiments in the dependent claims.

In response, the Office regrets any confusion regarding the claim groupings. The Office had no intention of limiting the scope of claims that recite generic embodiments. The reason that claims 1, 2, 9-14 and 24-28 were included in each of Groups I-IV is that they are *linking claims*. Claims 29, 30 and 39-41 should have also been included as linking claims between Groups I-IV. The next paragraph details more clearly what was originally intended by the restriction requirement.

Claims 1, 2, 9-14, 24-30 and 39-41 link inventions I-IV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 2, 9-14, 24-30 and 39-41. The inventions of Groups I-IV (reflective of the original groupings without the linking claims) are as follows:

- Group I (derivative of an effector molecule): claim 3
- Group II (antibody): claims 4-6, 15-21 and 32-37
- Group III (mannosylated molecule): claims 7, 8, 22 and 23

- Group IV (recombinant protein): claim 31

Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Regarding the restriction requirement, Applicant also requests clarification whether claims 39-42 were to be restricted to Ebola, HIV or SIV, or whether all of claims 1-41 were also to be restricted to Ebola, HIV or SIV. In response, only claims 39-41 are restricted to either Ebola, HIV or SIV. Claim 42 will only be examined if HIV is elected, since claim 42 is drawn to an embodiment of HIV. Applicant also argues that the Office has not demonstrated a serious burden of examination of Ebola, HIV and SIV. In response, the Office indicated that searches for Ebola, HIV and SIV are divergent. Ebola, HIV and SIV are different immunodeficiency viruses having different viral pathologies. While HIV and SIV both immunodeficiency viruses and classified similarly, literature that speaks to HIV will not necessarily discuss SIV and vice versa. Further, methods of treating HIV and SIV are not one and the same. SIV is the closest animal model of HIV infection, however, SIV is not an accepted animal model for predicting

HIV treatment in humans. Ebola is not an immunodeficiency virus. Literature that speaks to treatments of Ebola will not likely discuss a treatment for SIV or HIV and vice versa. Therefore, searching methods of treating/preventing Ebola, HIV and SIV places a serious burden on the Office.

Therefore, the restriction requirement as clarified above is deemed proper and made FINAL. Claims 1-80 are pending. Claims 4-8, 14-24, 31-38 and 43-80 are withdrawn from consideration, being drawn to non-elected inventions. Claims 1-3, 9-14, 24-30 and 39-42 are under examination.

Information Disclosure Statement

2. The information disclosure statement filed May 26, 2004 is acknowledged and a copy is attached to this Office action. Note that Patent Application numbers 10/464,531 and 10/700,491 have been considered but will not be printed on the face of the file of any patent that will issue.

Claim Objections

3. Claims 1, 24 and 39 are objected to for failing to spell out the acronyms DC-SIGN, CMV and HIV at their first occurrence, respectively. Claims 39, 40 and depending claims 41 and 42 are objected to for reciting non-elected inventions (Ebola and SIV) that are not eligible for rejoinder at any point in the future prosecution of this application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a cytomegalovirus (CMV) infection, does not reasonably provide enablement for preventing CMV infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The breadth of the claims encompasses a method of preventing CMV infection *in vivo*. The nature of the invention is the prevention of CMV infection by blocking CMV envelope protein from binding to DC-SIGN, thereby preventing viral entry and infection. The state of the art teaches that there is no safe and effective vaccine for CMV. The Centers for Disease Control (CDC)[i] reports that there are no vaccines for CMV because a vaccine strategy remains in the research and development phase. Wang *et al.* (*J. Virol.* 2004, 78(8):3965-3976, herein, "Wang") teaches that a CMV vaccine remains elusive and there is no acceptable model for this virus pathology (abstract). Wang states that "[S]ince CMV strains are severely host restricted, there is no animal protection model available to test the protective value of a human CMV vaccine", (page 3974, column 2, last paragraph). MacDonald *et al.* (*J. Virol.* 1998, 72(1) :442-451, herein, "MacDonald") teaches that vaccination with live human CMV (HCMV) can lessen disease severity in renal transplant recipients, but that the level of protection provided by the live virus is probably less than that afforded by the natural infection with HCMV (page 448, second column, first full paragraph). The level of skill in the art is high. The level of predictability in the art is low, evidenced by the above discussion. There is no guidance or working examples in the specification demonstrating

prevention of CMV infection in an acceptable animal model. It would require undue experimentation to use the claimed invention for preventing CMV infection in humans. Therefore, the claims are not enabled for their full scope.

5. Claims 39, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating human immunodeficiency virus (HIV) infection, does not reasonably provide enablement for preventing HIV infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The breadth of the claims is unreasonable, encompassing prevention of HIV infection *in vivo*. The nature of the invention is the prevention of HIV by inhibiting HIV gp120 from binding to cells expressing DC-SIGN, thereby preventing viral entry and infection. The state of the art shows *treatments* that reduce viral entry by inhibiting gp120 from binding CD4 receptors on T cells. Greene (*Nature Immunology*, 2004, 5(9):867-871) discloses that HIV attachment inhibitors, which block gp120 from binding to the CD4 receptor, are effective for reducing viral load (Greene, page 867, second and third column). However, the state of the art also teaches that there are no preventative treatments for HIV. Desrosiers (*Nature Medicine*, March 2004, 10(3):221-223) teaches that the natural immune response to HIV-1, humoral and T-cell responses, are ineffective due to antigenic variation/mutation, resistance to antibody-mediated neutralization, down regulation of major histocompatibility class I molecules from the surface of infected cells and destruction of $CD4^+$ T helper cells (page 221, cols. 1-2). Vaccine strategies for protecting rhesus monkeys from SIV, the closest animal model to HIV-1 infection in humans, yet

unacceptable, has been unsuccessful. The variability of sequences among HIV-1 isolates is enormous, making it impossible to date to construct epitopes that are neutralizing across HIV-1 isolates. Vaccine trials using peptide vaccines against HIV-1 using recombinant gp120 have failed to induce protective immunity (page 222, col. 1). Feinberg *et al.* (*Nature Medicine*, March 2002, 8(3):207-210, herein, "Feinberg") discloses that there are no acceptable animal models that reflect the actual biological pathology of HIV-1 in humans. Rhesus monkeys cannot be infected with HIV-1, so chimeric constructs of HIV and SIV are used. Unfortunately, this model of infection, while useful, does not reflect HIV-1 infection/pathology in humans in many respects. The main drawback of this model is that promising responses in the model are not direct translations into success in humans. For example, the rapid $CD4^+$ T helper cell depletion in the animal model is due to the nature of viral entry, which primarily uses the CXCR4 viral coreceptor. This is not consistent with the majority of HIV-1 viruses transmitted between humans which uses the CCR5 coreceptor, resulting in slower depletion of $CD4^+$ T helper cells in humans. The use of different coreceptors is an important consideration for designing vaccines in humans (page 208). Further, the SHIV model is sensitive to autologous neutralizing antibodies, whereas most primary HIV-1 isolates resist antibody neutralization (page 208-209, bridging paragraph). The level of skill in the art is high. The level of predictability in the art regarding HIV treatments *in vivo* is low, evidenced by the above discussion. There is no guidance in the specification or working examples demonstrating prevention of HIV in an acceptable animal model. It would require undue experimentation to use the claimed inventive method to prevent HIV infection. Therefore, the claims are not enabled for their full scope.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 9-14, 24-30 and 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite that the DC-SIGN modulator is administered in an amount sufficient to "substantially" modulate/inhibit binding of the effector molecule to DC-SIGN. It is unclear what the metes and bounds are of the amount of modulator required to substantially modulate/inhibit binding. The specification does not clearly define what amount results in a substantial modulation or inhibition of binding. There should be endpoints indicating that a substantial level of modulation/inhibition has been achieved.

Further, claim 3 recites, "a blocking derivative of the effector molecule". It is unclear what a derivative of the effector molecule is. How is this blocker derived from the effector molecule? The Office understands that the effector molecule is what binds to DC-SIGN, and that the derivative of the effector molecule will block binding between the effector molecule and DC-SIGN. However, the specification does not define what the derivative of the effector molecule actually is or what it binds to. Does the derivative bind the effector molecule or DC-SIGN? The Office cannot conduct a meaningful search of the prior art on this term due to its indefiniteness. Clarification is required.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 9-14, 39, 40 and 42 are rejected under 35 U.S.C. 102(a) as being anticipated by Littman *et al.* (WO 01/64752 A2). The claims are drawn to a method of treating a disease of a mammal, wherein at least one symptom of the disease is mediated at least in part by the binding of an effector molecule to a DC-SIGN receptor of the mammal to be treated, wherein the method comprises administering to the mammal an amount of a DC-SIGN modulator sufficient to substantially modulate the biding of the effector molecule to the DC-SIGN receptor to thereby treat the disease. (Note that the claims also recite prevention of disease, however, the claims are only enabled for treatment of disease and are therefore presently only treated for their enabled embodiment.) Specifically, the DC-SIGN modulator is a blocker that inhibits the binding of the effector molecule to the DC-SIGN receptor. "DC-SIGN receptor" and "DC-SIGN" are synonymous terms because DC-SIGN is a receptor. The DC-SIGN blocker is a blocking derivative of the effector molecule. (As noted above, the identity of a blocking derivative of the effector molecule is not clearly defined. In the interests of compact prosecution, the blocker has been treated as anything that binds to the effector molecule.) More specifically, the disease being treated is a viral disease, wherein the viral effector molecule is a molecular constituent of the viral envelope, such as envelope glycoprotein. The viral disease can be HIV infection in a human.

Littman *et al.* discloses antibodies (a blocking derivative of the effector molecule) specific for the antigenic fragment of gp120 (envelope subunit protein of HIV and binding

moiety of viral effector molecule) that inhibits DC-SIGN on dendritic cells from interacting with gp120. Also disclosed are methods of treating HIV infection by administering antibodies that bind to gp120, thereby inhibiting binding of gp120 to DC-SIGN. (See Littman *et al.*, page 5, pages 5-6, bridging paragraph, and claims 1-4.) Therefore, Littman *et al.* anticipates the claims.

8. Claims 1-3, 9-14, 39, 40 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Figdor *et al.* (EP 1046651 A1, herein, "Figdor"). The claims are drawn to a method of treating a disease of a mammal, wherein at least one symptom of the disease is mediated at least in part by the binding of an effector molecule to a DC-SIGN receptor of the mammal to be treated, wherein the method comprises administering to the mammal an amount of a DC-SIGN modulator sufficient to substantially modulate the biding of the effector molecule to the DC-SIGN receptor to thereby treat the disease. (Note that the claims also recite prevention of disease, however, the claims are only enabled for treatment of disease and are therefore presently only treated for their enabled embodiment.) Specifically, the DC-SIGN modulator is a blocker that inhibits the binding of the effector molecule to the DC-SIGN receptor. The DC-SIGN blocker is a blocking derivative of the effector molecule. (As noted above, the identity of a blocking derivative of the effector molecule is not clearly defined. In the interests of compact prosecution, the blocker has been treated as anything that binds to the effector molecule.) More specifically, the disease being treated is a viral disease, wherein the viral effector molecule is a molecular constituent of the viral envelope, such as envelope glycoprotein. The viral disease can be HIV infection in a human.

Figdor discloses a method for treating HIV infection in humans comprising administering humanized monoclonal antibodies (modulator/blocker) that bind DC-SIGN on dendritic cells. The binding of DC-SIGN prevents HIV gp120 (binding moiety of viral effector molecule) from interacting with DC-SIGN (page 4, [0040], page 5, [0046] and page 7, [0070]-[0071]). Therefore, the claims are anticipated by Figdor.

9. Claims 1-3, 9-14, 24-30 and 39-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Gehrz *et al.* (WO 91/05876, herein, "Gehrz"). The claims are drawn to a method of treating a disease of a mammal, wherein at least one symptom of the disease is mediated at least in part by the binding of an effector molecule to a DC-SIGN receptor of the mammal to be treated, wherein the method comprises administering to the mammal an amount of a DC-SIGN modulator sufficient to substantially modulate the biding of the effector molecule to the DC-SIGN receptor to thereby treat the disease. (Note that the claims also recite prevention of disease, however, the claims are only enabled for treatment of disease and are therefore presently only treated for their enabled embodiment.) Specifically, the DC-SIGN modulator is a blocker that inhibits the binding of the effector molecule to the DC-SIGN receptor. The DC-SIGN blocker is a blocking derivative of the effector molecule. (As noted above, the identity of a blocking derivative of the effector molecule is not clearly defined. In the interests of compact prosecution, the blocker has been treated as anything that binds to the effector molecule.) More specifically, the disease being treated is a viral disease, such as cytomegalovirus (CMV) wherein the viral effector molecule is a molecular constituent of the viral envelope, such as envelope

glycoprotein B. The claimed method can also treat HIV disease/infection in a human using the CMV glycoprotein B blocking derivative.

Gehrz discloses a method for treating human CMV with a cocktail of monoclonal antibodies, one of which binds to gp55, a subunit of envelope glycoprotein B (abstract and Example 1). The method can be practiced on human patients with HCMV infections, including those with acquired immune deficiency (AIDS). The antibodies include humanized antibodies (page 36-37, bridging paragraph). Although Gehrz does not mention that the monoclonal antibodies bind to DC-SIGN to interrupt binding between glycoprotein B and DC-SIGN, Gehrz's antibodies are inherently interacting with DC-SIGN. When Gehrz administers the antibody cocktail to an AIDS patient (infected with HIV), the antibody cocktail is inherently acting on DC-SIGN. Therefore, the claims are anticipated by Gehrz.

Double Patenting

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The

filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 2, 9-14, 39, 40 and 42 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 9-14, 38, 39 and 41 of copending Application No. 10/700,491. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

11. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B Chen

Stacy B. Chen
December 21, 2004

[i] CDC, National Center for Infectious Diseases Cytomegalovirus (CMV) Infection, available from website: http://www.cdc.gov/ncidod/diseases/cmv.htm